Supplementary Materials and Methods

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This supplementary material has been provided by the authors to give readers additional information about their work.

Appendix 1. Detailed information on participants, interventions, assessments, and statistical analyses

Participants

Eligible participants were interviewed and diagnosed by board-certified psychiatrists using the Mini-International Neuropsychiatric Interview (MINI) [1]. Only those with a Hamilton Depression Rating Scale (17-items, HAM-D) score ≥ 17 [2] and low suicide risk (MINI) were included. The exclusion criteria included other neuropsychiatric conditions (except for anxiety disorders as comorbidity), pregnancy, specific contraindications to tDCS (e.g., metal plates in the head), and participation in previous tDCS trials. All patients had been escitalopram-naïve, as escitalopram was the active comparator, and free of antidepressant medications for at least 5 half-lives of the drug—at least 2 weeks for venlafaxine and paroxetine, due to withdrawal symptoms, and 5 weeks for fluoxetine.

Interventions

We used customized Soterix devices (devices, sponges and headgears [EASYstrap], SoterixMedical, New York, NY) to perform the tDCS sessions. The parameters were: 2mA current intensity, 25cm^2 saline-soaked sponges (current density = 0.8 A/m^2), 30 min/day, with the anode and the cathode positioned over the left and right DLPFC, respectively, targeted using the "Omni-Lateral-Electrode" method [3]. Ramp-up and ramp-down periods of 30 and 15 seconds were employed. TDCS sessions were performed by trained nurses.

Escitalopram was chosen due to its efficacy, tolerability, availability, and cost [4]. The placebo pill had the same color, appearance, taste and size as escitalopram.

Statistical analyses

The optimal number of trajectories and optimal polynomial degree were determined using the improvement in model fit, represented by the Bayesian information criterion (BIC). We used the BIC log Bayes factor approximation, defined as two times the difference in BIC between a more complex versus a less complex model for model selection. The BIC log Bayes factor has been demonstrated to be an acceptable approximation to the log Bayes factor criterion [5]. When it exceeded more than 10 points in difference, the model with a higher degree of complexity was favored [6].

The optimal parameters were determined by systematically reducing the number of trajectory classes and polynomial degree for each trajectory until models reached a single class with linear polynomial degree.

Criteria for overall model adequacy were reported (Akaike Information Criterion, BIC, entropy, relative-entropy).

A priori selected variables were entered into the multinomial logistic regression models simultaneously.

We explored potential novel predictors of response using a data-driven approach that included all available clinical information from the trial (k=51 predictors), such as syndrome-specific rating scales (TCI, MADRS, BDI), and also demographic and clinical variables. To avoid issues related to large numbers of predictors and multicollinearity in combination with (e.g. multicollinearity, lack of power), wea variable pre-selection procedure was performed a stability ranking procedure in combination with elastic net regularization [7]. The approach has two effects: it shrinks coefficients of correlated predictors towards each other, and removes uninformative variables from the model. While other approaches for high numbers of predictors have been heavily criticized for overfitting the data (e.g., stepwise regression, selection based on significance of univariate correlation), this procedure makes the selection

process more reliable by adding resampling to the variable selection, hence avoiding fitting only one model but fitting many different ones on subsets. We derived features from 1000 iterations of elastic net regularization using 3-fold cross-validation to find optimal proportions between penalization (least absolute shrinkage and selection operator, LASSO) and regularization (Tikhonov regularization, also known as ridge-regression). Elastic net models were run on k-nearest-neighbor imputed (k=5) predictor variables [8], as they do not support missing data [9].

To avoid circularity, no confirmatory modeling of the identified associations was applied. Instead the features are presented ranked by their selection stability to provide points of reference in the planning of future confirmatory studies. As proxies for relevance and directionality of effects, we supplied each feature's selection probability across the hyperparameter space and log-odds with 99.9% confidence intervals (i.e. adjusted for the total number of features), respectively.

Table S1. Additional baseline information about patients receiving tDCS + placebo, escitalopram + sham tDCS and placebo + sham tDCS for depression, by symptom trajectory class

	tDCS + placebo, m (SD)			Escitalopram + sham tDCS, m (SD)			Placebo + sham tDCS, m (SD)		
Characteristic	**rapid (N=41)**	**slow (N=31)**	**no/minimal (N=22)**	**rapid (N=23)**	**slow (N=52)**	**no/minimal (N=12)**	**rapid (N=26)**	**slow (N=24)**	**no/minimal(N=10)**
Family and employment									
Schooling — yr	15.26 (5.47)	15.04 (4.99)	15.58 (3.69)	13.83 (3.95)	15.42 (4.09)	14.91 (4.09)	15.59 (4.57)	16.12 (3.3)	15.56 (3.61)
Married — no. (%)	22 (54)	16 (52)	9 (41)	9 (39)	22 (42)	5 (42)	12 (46)	4 (17)	1 (10)
Unemployed — no. (%)	9 (22)	10 (32)	9 (41)	4 (17)	16 (31)	4 (33)	9 (35)	3 (12)	5 (50)
History of depression									
Family history of depression — no. (%)	30 (73)	19 (61)	15 (68)	17 (74)	31 (60)	6 (50)	15 (58)	17 (71)	7 (70)
Clinical characteristics									
Smoker — no. (%)	10 (24)	3 (10)	5 (23)	8 (35)	14 (27)	4 (33)	1 (4)	7 (29)	3 (30)
BMI	25.68 (4.49)	26.24 (5.59)	24.65 (4.18)	27.67 (4.08)	27.02 (6.56)	25.79 (3.29)	26.91 (5.62)	26.05 (6.23)	25.22 (5.66)
Hypertension — no. (%)	8 (20)	9 (29)	4 (18)	7 (30)	8 (15)	3 (25)	6 (23)	4 (17)	3 (30)

Diabetes — no. (%)	2 (5)	2 (6)	NA (NA)	3 (13)	8 (15)	2 (17)	5 (19)	1 (4)	NA (NA)
Hypothyroidism — no. (%)	7 (17)	5 (16)	2 (9)	4 (17)	5 (10)	2 (17)	NA (NA)	1 (4)	NA (NA)

Note: BMI Body mass index

Table S2. Posterior classification for patient groups treated with tDCS + placebo, escitalopram + sham tDCS, and placebo + sham tDCS

	tDCS + placebo			Escitalopram + sham tDCS				Placebo + sham tDCS		
	rapid	**slow**	**no/minimal**	**rapid**	**slow**	**late**	**no/minimal**	**rapid**	**slow**	**no/minimal**
N	41.00	31.00	22.0	23.00	52.00	4.0	12.00	26.00	24	10.00
%	43.62	32.98	23.4	25.27	57.14	4.4	13.19	43.33	40	16.67

Note: Assessing the clinical meaningfulness of the trajectory patterns, aiming to include classes with at least 5% capture of the population

Table S3. Model and class specific fit indices for optimal latent class solutions in patient groups treated with tDCS + placebo, escitalopram + sham tDCS, and placebo + sham tDCS

	Model specific				Class specific	
Treatment/Class	**AIC**	**BIC**	**Entropy**	**Relative Entropy**	**APPA**	**OCC**
tDCS + placebo	3373.67	3404.19	24.86	0.76		
rapid improvement (N=41)					0.916	15.428
slow improvement (N=31)					0.851	10.653
no/minimal improvement (N=22)					0.857	19.176
Escitalopram + sham tDCS	3218.17	3258.35	26.43	0.79		
rapid improvement (N=23)					0.873	19.211
slow improvement (N=52)					0.867	5.541
late improvement (N=4)					0.988	1398.018
no/minimal improvement (N=12)					0.851	35.236
Placebo + sham tDCS	2334.89	2360.02	12.44	0.81		
rapid improvement (N=26)					0.932	18.579
slow improvement (N=24)					0.912	14.557

no/minimal improvement (N=10)					0.878	37.029
Recommendation	relative/small	relative/small	close to 0	close to 1	>.70	>5

Note: AIC Akaike information criterion; BIC Bayesian information criterion; APPA average maximum posterior probability of assignments; OCC odds of correct classification

Table S4. Mean of posterior probabilities in each class for patient groups treated with tDCS + placebo, escitalopram + sham tDCS, and placebo + sham tDCS

	Probability 1	Probability 2	Probability 3	Probability 4
tDCS + placebo				
rapid improvement	0.9156	0.0810	0.0034	NA
slow improvement	0.0406	0.8513	0.1081	NA
no/minimal improvement	0.0005	0.1428	0.8567	NA
Escitalopram + sham tDCS				
rapid improvement	0.8731	0.1261	0.0000	0.0008
slow improvement	0.0752	0.8673	0.0103	0.0472
late improvement	0.0001	0.0079	0.9880	0.0040
no/minimal improvement	0.0000	0.1009	0.0480	0.8511
Placebo + sham tDCS				
rapid improvement	0.9315	0.0684	0.0000	NA
slow improvement	0.0476	0.9116	0.0408	NA
no/minimal improvement	0.0000	0.1221	0.8779	NA

Note: Mean posterior probability in same class should not be <0.70

Table S5. Posterior probabilities above a threshold (%) for patient groups treated with tDCS + placebo, escitalopram + sham tDCS, and placebo + sham tDCS

	tDCS + placebo			Escitalopram + sham tDCS				Placebo + sham tDCS		
Cutoff	**rapid**	**slow**	**no/minimal**	**rapid**	**slow**	**late**	**no/minimal**	**rapid**	**slow**	**no/minimal**
Prob >0.7	85.37	77.42	77.27	78.26	78.85	100	75.00	96.15	91.67	80
Prob >0.8	82.93	74.19	68.18	69.57	67.31	100	58.33	80.77	83.33	70
Prob >0.9	73.17	61.29	54.55	65.22	59.62	100	58.33	69.23	66.67	60

Table S6: Response and remission rates for distinct trajectory classes within each treatment arm

		tDCS + placebo				Escitalopram + sham tDCS				Placebo + sham tDCS			
Outcome	**Total Sample**	**rapid (N=41)**	**slow (N=31)**	**no/minimal (N=22)**	**P-Value**	**rapid (N=23)**	**slow (N=52)**	**no/minimal (N=12)**	**P-Value**	**rapid (N=26)**	**Slow (N=24)**	**no/minimal (N=10)**	**P-Value**
Response, n (%)													
Week 1	49 (20.33)	18 (43.9)	1 (3.23)	0 (0)	<.001	11 (47.83)	9 (17.31)	0 (0)	0.003	7 (26.92)	3 (12.5)	0 (0)	0.147
Week 2	65 (26.97)	17 (41.46)	2 (6.45)	0 (0)	<.001	15 (65.22)	16 (30.77)	1 (8.33)	0.001	11 (42.31)	3 (12.5)	0 (0)	0.004
Week 3	79 (32.78)	24 (58.54)	5 (16.13)	0 (0)	<.001	12 (52.17)	20 (38.46)	0 (0)	0.002	15 (57.69)	2 (8.33)	1 (10)	<.001
Week 6	80 (33.2)	19 (46.34)	4 (12.9)	1 (4.55)	<.001	17 (73.91)	17 (32.69)	1 (8.33)	<.001	17 (65.38)	3 (12.5)	1 (10)	<.001
Week 8	83 (34.44)	23 (56.1)	8 (25.81)	0 (0)	<.001	18 (78.26)	19 (36.54)	0 (0)	<.001	13 (50)	2 (8.33)	0 (0)	<.001
Week 10	79 (32.78)	27 (65.85)	5 (16.13)	1 (4.55)	<.001	19 (82.61)	13 (25)	1 (8.33)	<.001	13 (50)	0 (0)	0 (0)	<.001
Remission, n (%)													
Week 1	18 (7.47)	13 (31.71)	0 (0)	0 (0)	<.001	2 (8.7)	1 (1.92)	0 (0)	0.252	2 (7.69)	0 (0)	0 (0)	0.655
Week 2	29 (12.03)	7 (17.07)	0 (0)	0 (0)	0.006	12 (52.17)	5 (9.62)	0 (0)	<.001	4 (15.38)	1 (4.17)	0 (0)	0.252
Week 3	42 (17.43)	16 (39.02)	2 (6.45)	0 (0)	<.001	10 (43.48)	5 (9.62)	0 (0)	<.001	9 (34.62)	0 (0)	0 (0)	0.001
Week 6	40 (16.6)	13 (31.71)	1 (3.23)	0 (0)	<.001	13 (56.52)	5 (9.62)	1 (8.33)	<.001	7 (26.92)	0 (0)	0 (0)	0.004
Week 8	52 (21.58)	18 (43.9)	2 (6.45)	0 (0)	<.001	17 (73.91)	4 (7.69)	0 (0)	<.001	9 (34.62)	2 (8.33)	0 (0)	0.006

Week 10	52 (21.58)	21 (51.22)	0 (0)	0 (0)	<.001	17 (73.91)	6 (11.54)	0 (0)	<.001	8 (30.77)	0 (0)	0 (0)	0.005

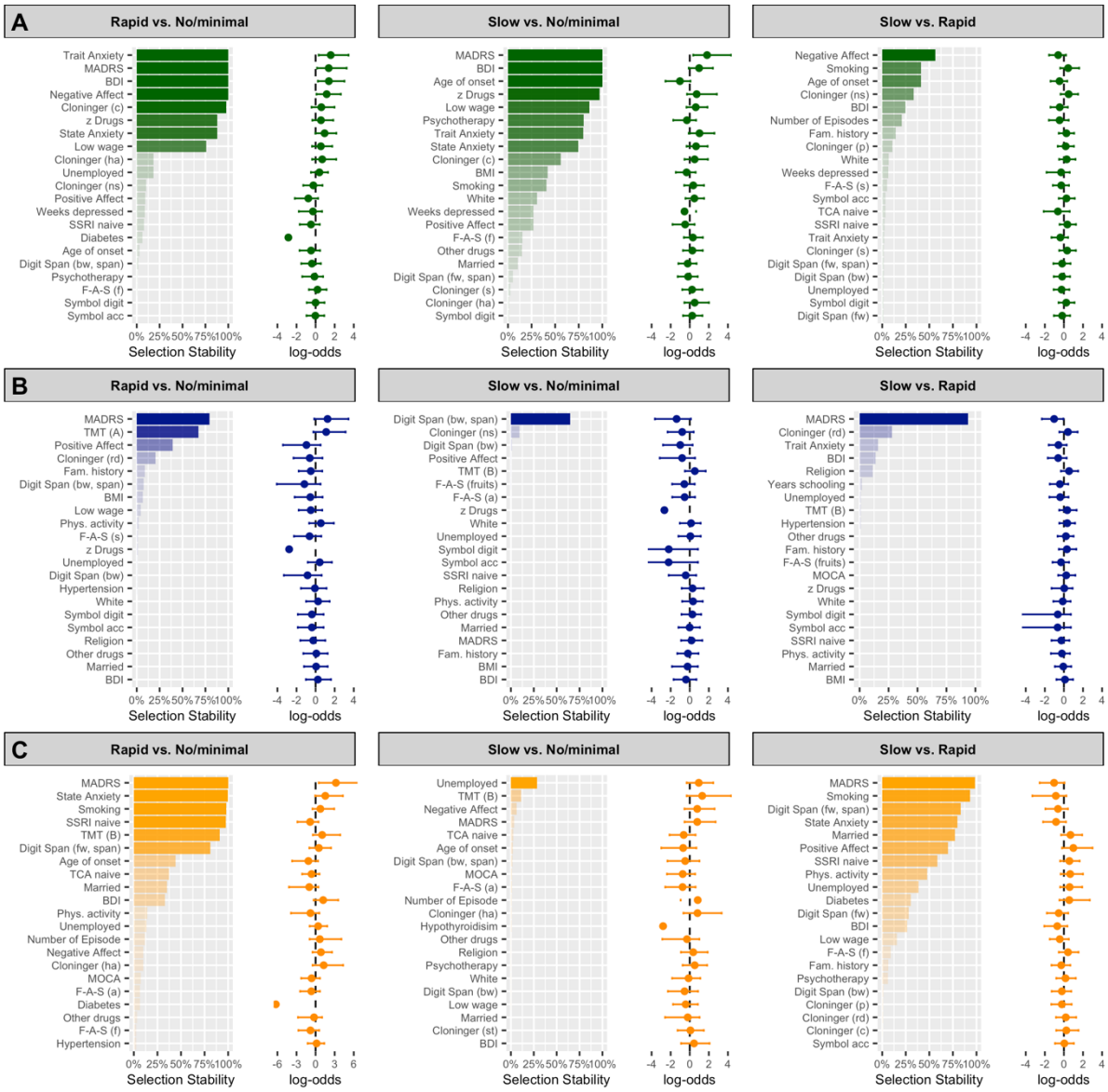
Note: Response was defined as a reduction ≥50% from baseline in HAM-D scores, and remission was defined as a HAM-D score ≤7; P-values represent result of χ^2-test or Fisher's exact test comparing membership ratios between trajectories; P-values were FDR corrected for the number of repeated measurements.

Table S7. Results of Hosmer-Lemeshow tests for goodness of fit in multinomial regression models within each treatment arm

Selection	Treatment	χ^2	df	P
Top-down	tDCS + **placebo**	14.67	16	0.549
Top-down	Escitalopram + **sham tDCS**	19.09	16	0.264
Top-down	Placebo + **sham tDCS**	11.77	16	0.760

Note: df degrees of freedom; non-significant P-value is indicative for similar observed and expected frequencies, i.e. good model fit

Figure S1. Top ranked features from stability selection procedure using elastic net regularization



Note: (A) tDCS (B) escitalopram (C) placebo; X-axis represents selection probability throughout 1000 iterations of elastic net regularization with 3-fold cross-validation in order to find optimal proportions of penalization and regularization; Log-odds and 99.9% confidence intervals are displayed as proxies for relevance and direction of effect. Log-odds < 0 and > 0 are numerically associated with 1st and 2nd named group, respectively. Predictors with without log-odds confidence intervals had zero-events, thus lower bounds could not be estimated. A total of k=51 predictors were included in the analysis, Predictors that are not displayed were selected 0 times. Results of the bottom-up analysis are strictly exploratory and should not be interpreted as confirmatory.

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